REMARKS

I. The Rejections of Record

Pending claims 29-97 have been finally rejected under 35 U.S.C. § 103(a) over three separately stated combinations of references:

- The November 1997 package insert for RITUXAN® ("RITUXAN® package insert") (referred to as "IDEC Pharmaceuticals Corp." in the Office action) in view of U.S. Patent No. 5,843,398 ("Kaminski '398 patent"), U.S. Patent Application Publication No. 2003/ 0018014 ("Lerner"), and *Breast Cancer Res. Treatment*, 25:57-63 (1993) ("Stenbygaard");

- *J. Clin. Oncol.*, 16(8): 2825-2883 (1998) ("McLaughlin") in view of Kaminski '398 patent, U.S. Patent No. 6,090,365 ("Kaminski '365 patent"), Lerner and Stenbygaard; and

- U.S. Patent No. 5,736,137("Anderson patent") in view of Kaminski '398 patent, Kaminski '365 patent, and Stenbygaard.

The Examiner, in the rejection dated 29 May 2008, characterized each of the three primary references cited in the three rejections of record as describing administration of a chimeric anti-CD20 antibody for the treatment of patients with "relapsed or refractory CD20 positive cancers," "several types of lymphoma" or "B-cell cancer." See 29 May 2008 Rejection, pages 3-4 (describing the RITUXAN® package insert), pages 5-6 (describing McLaughlin), and page 8 (describing the Anderson patent), respectively. In each instance, the Examiner observed that the primary reference did not teach treatment of CLL patients by administration of anti-CD20 antibodies, nor did it teach treatment of CLL patients refractory to fludarabine, administration of the antibody in all of the designated dosages, or administration in combination with chemotherapeutic agents including chlorambucil, methotrexate, toremifine, tamoxifen and cisplatin. See 29 May 2008 rejection, pages 4, 6, and 8.

The Examiner, nonetheless, concluded the claimed methods would have been obvious to a person of ordinary skill in the art in 1998 when each of the primary references was considered with certain secondary references. In particular, the

Examiner cited one or both of the Kaminski patents and Stenybygaard in each of the three rejections under §103(a), and has additionally cited Lerner in support of two of the rejections (i.e., those based on the RITUXAN® package insert and McLaughlin).

In the Final Action, the Examiner has maintained the rejections of record despite the evidence provided by Applicant, including Dr. Schenkein's first declaration under 37 C.F.R. § 1.132, signed 14 November 2008 ("Schenkein 1st"). The Examiner concludes that, despite the arguments of Applicant and the evidence presented, "while the primary references teach the administration of the CD20 antibody rituximab to B cell cancers other than CLL, the combination of references does not preclude the instant rejection." In particular, the Examiner states that "the declaration under 37 C.F.R. § 1.132 filed December 1, 2008 is insufficient to overcome the rejection under 35 U.S.C. 103(a) because it does not provide a showing of good and sufficient reasons why one of ordinary skill in the art would not be motivated to try implementing a mode of therapy, which has been successful in one B cell cancer treatment, in another B cell cancer treatment." See Final Action at page 4.

The Examiner makes a number of specific conclusions in support of her decision to maintain the rejections at pages 4 to 7 of the Final Action. First, the Examiner states that a person of ordinary skill in the art would have had a reasonable expectation of success in treating CLL using anti-CD20 antibodies based on the showing of "effectiveness of CD20 therapy for a B cell cancer and the high expression of CD20 antigen on CLL (more than 95% expression on patients with CLL)" citing the Kaminski '398 patent, at column 8, lines 9-16. Second, the Examiner states that "while the declarant [Dr. Schenkein] suggests there would be decreased therapeutic efficacy that suggestion is not equivalent to there would be no therapeutic effectiveness." In other words, the Examiner appears to have (incorrectly) interpreted Dr. Schenkein's earlier testimony as being that a person of ordinary skill would have believed that anti-CD20 antibodies would have been partially effective in treating CLL. Finally, the Examiner states there is "no factual evidence presented suggestive of failure of treatment of CLL in a patient" and that "the term, treatment reads broadly on a process of implementing

therapy to modify, alter or remedy a health problem." The Examiner concludes by stating:

> Differences between CLL and NHL do not teach away from the desirability of doing what the inventor has done. Applicants and Declarant have not presented sufficient evidence teaching the immunotherapeutic mechanisms, host effector functions and receptor binding affinity of the CD20 antibody would differ between the two diseases, resulting in different antitumor mechanisms and significant differences in the impact of the therapy.

Applicant respectfully submits that the factual assumptions of the Examiner are inconsistent with the evidence of record and the currently provided evidence. As a consequence, Applicant submits that the rejections of the claims under 35 U.S.C. § 103 are improper, and accordingly respectfully requests withdrawal of those rejections.

II. Second Declaration of Dr. Schenkein

Applicant provides the accompanying second declaration under 37 C.F.R. § 1.132 of Dr. David Schenkein signed 5 May 2009 ("Schenkein 2nd") in response to the specific criticisms by the Examiner of Dr. Schenkein's first § 1.132 declaration in the Final Action. Applicant submits that Dr. Schenkein's second declaration satisfies the requirements of 37 CFR § 1.116(c) as it responds directly to the specific scientific assertions by the Examiner that were first articulated in the Final Action, and is therefore entitled to consideration.

Dr. Schenkein is well-qualified to express opinions about the views of a person of ordinary skill in November of 1998. At that time, he was a practicing oncologist with actual experience in treating CLL patients, and was familiar with rituximab and its use in treating Non-Hodgkin's Lymphoma (NHL) patients. He is able to describe the perspectives of a person of ordinary skill in the art based on his own personal experiences from that time. Moreover, Dr. Schenkein has provided detailed reasoning and citations to relevant scientific literature to support the opinions he provided in each of his declarations under 37 C.F.R. § 1.132. Accordingly, Applicant requests the Examiner to consider favorably the evidence provided by Dr. Schenkein in his declarations under § 1.132.

III. The Cited Prior Art Is Incorrectly Characterized

The three primary references cited by the Examiner (i.e., the RITUXAN® package insert, McLaughlin and Anderson patent) each disclose the use of rituximab to treat NHL. As acknowledged by the Office, none of these references discloses or suggests that rituximab could or should be used to treat CLL. See generally Schenkein 1st at ¶¶ 6-9.

As Dr. Schenkein has explained, CLL and NHL are very different diseases, presenting very different cellular and physiological characteristics, and implicating different therapeutic strategies. See generally, Schenkein 1st at ¶¶ 18-27, and Hoffman (1995) (cited therein). The Examiner's central assumption regarding the cited references – that successful treatment of a B cell lymphoma (NHL) with rituximab would lead a person of ordinary skill to expect comparable success in treating CLL, a different B-cell "cancer" – conflicts with the substantial amount of evidence of record on this point, as explained further below.

Applicant also submits that the Examiner has incorrectly characterized the actual content and teachings of each of the cited references.

RITUXAN® package insert: The Examiner states that the RITUXAN® package insert "speaks to the applicability of implementing combination therapy comprising rituximab and CHOP to patients with CD20 positive cancers." See Final Action at page 4. In fact, the 1997 RITUXAN® package insert is confined to the treatment of relapsed or refractory low-grade or follicular NHL using rituximab and makes no mention of treating "CD20 positive cancers" generally (see "Indications and Usage"). Moreover, the regulatory approval reflected in the package insert is for rituximab administered as a single agent, i.e. without CHOP. See RITUXAN® package insert under "Clinical Studies" as well as "Dosage and Administration."

Anderson patent: The Examiner states at page 5 of the Final Action that the Anderson patent "teaches therapeutic methods designed for the general treatment of B cell disorders including CLL" (emphasis added). The quoted portion of the Anderson patent actually reads "[d]isclosed herein are therapeutic methods designed for the

treatment of B cell disorders, and in particular B cell lymphomas" (column 5, lines 19-21). There is no mention in the Anderson patent of treatment of CLL using anti-CD20 antibodies or other agents.

McLaughlin: The Examiner appears to maintain her position that McLaughlin teaches and suggests administration of rituximab to treat a variety of B-cell lymphomas, alone or in combination with cytotoxic agents. See, e.g., Office Action of 29 May 2008 at pages 5-6. In response to Applicant's observation that McLaughlin specifically excluded CLL patients from the clinical trials reported in the paper, the Examiner states that this "seems to be more a reflection of streamlining the patient population for testing and not a reflection of inefficiency of treatment to the CLL patient population." Final Action at page 4. There is nothing, however, in McLaughlin that supports this conclusion. Instead, the more plausible scientific explanation for why CLL patients were excluded was that "the authors believed that administration of anti-CD20 antibodies to CLL patients would place them at risk of serious side effects with no prospect for positive clinical benefits." See Schenkein 2nd at ¶ 31.

Kaminski patents: The Examiner portrays the Kaminski patent disclosure as teaching methods of treating B cell cancers using unlabeled anti-CD20 antibodies. This is inaccurate in several respects. Kaminski focuses on treatment of NHL using radiolabeled antibodies to CD20 to treat lymphomas, not CLL. See Schenkein 2nd at ¶ 19; Schenkein 1st at ¶11. Kaminski – read accurately – actually calls into question whether unlabeled antibodies could be used alone to effectively treat even lymphomas. For example, Kaminski states that "because of the limited efficacy of unmodified antibodies, recent attention has focused on the use of antibodies conjugated to cytotoxic agents" (Applicant's emphasis). See, e.g., Kaminski '398 at col. 2, lines 20-22; Schenkein 2nd at ¶ 24. Example IV of Kaminski actually reinforces this perspective. In Example IV, Kaminski hypothesizes that there may be a synergistic effect in cell killing when anti-CD20 antibodies bind to a lymphoma cell and the cells are concurrently exposed to a radioisotope. See Kaminski '398 at col. 35, lines 35-41 ("the excellent results described above for radioimmunotherapy using an anti-CD20 antibody might be due, in part, to synergism in the induction of apoptosis by binding of the anti-CD20

antibody and the irradiation of the tumor cell.") Example IV also does not indicate that a non-radiolabeled anti-CD20 antibody should be combined with a chemotherapeutic agent as suggested at page 5 of the Final Action (Schenkein 2nd at ¶ 22). In other words, Kaminski, when read accurately by a person of ordinary skill in the art, actually teaches away from the idea of treating CLL patients with non-radiolabeled anti-CD20 antibodies as required by claims 29, 55 and 97. See, e.g., Schenkein 2nd at ¶ 24.

Stenybygaard: The Examiner has characterized Stenybygaard as "teaching the implementation of chemotherapeutic agents, toremifene and tamoxifen, in the treatment of cancer." See 29 May 2008 Office Action, at pages 6 and 9. In reality, Stenybygaard only discusses approaches for treatment of advanced breast cancer, not cancers generally, and certainly not CLL. It also not only fails to disclose or suggest administering toremifene or tamoxifen with other agents, such as anti-CD20 antibodies, but actually cautions against combining drugs due to "clinical cross-resistance" between drugs (column 1 on page 62)

Lerner: The Examiner characterizes Lerner as teaching that while CLL patients may have initial clinical responses to alkylating agents such as fludarabine, these patients ultimately will become refractory to this type of therapy (See 29 May 2008 Office Action at page 4). In reality, Lerner describes treatment of CLL patients with chemical compounds that specifically inhibit Type 4 cyclic adenosine monophosphate phosphodiesterase, and in particular, the compound rolipram. There is no discussion in Lerner of treating CLL patients using anti-CD20 antibodies, or of using Type 4 inhibitors in combination with anti-CD20 - or other antibodies - to treat any type of cancer.

Thus, when read accurately, the cited references do not describe or suggest methods of treating CLL by administering an anti-CD20 antibody to a CLL patient in an amount effective to treat the CLL, particularly where the method does not include treatment with a radiolabeled antibody (claim 29) or where radiation is not used in conjunction with the therapeutic anti-CD20 antibody (claim 97) . Nor do the cited references describe or suggest the claimed dosage(s) required by certain of the claims

(e.g., claims 34 and 60), combination of an anti-CD20 antibody with chemotherapy to treat CLL (claims 55 and 60), or treatment of a fludarabine-refractory patient (claim 94).

IV. The Office has Erred Substantively as to Its Factual Findings

In order to properly reject a claim as being obvious over the prior art, the Examiner must accurately describe, among other things, the scope and content of the prior art, the differences between the claimed invention and the prior art, and why the claimed invention would have been obvious to a person of ordinary skill in the art at the time of the invention. See M.P.E.P. § 706.02(j). In this case, the Examiner has made significant factual errors concerning the scope and contents of the prior art, the differences between the claimed invention and the teachings of the prior art, and what the person of ordinary skill would have concluded from the prior art.

The primary error made by the Examiner was to mistakenly conclude that successful treatment of low grade or follicular NHL with an anti-CD20 antibody would have led a person of ordinary skill to believe that administration of such an antibody to a patient with any other type of B-cell cancer in which the B-cells express the CD20 antigen would have been similarly effective. The substantial evidence of record shows why a person of ordinary skill in the art would not have reached this conclusion, and actually shows is that it was surprising that one could effectively treat CLL patients with anti-CD20 antibodies, as explained below. Accordingly, because the rejections are based on incorrect scientific assumptions, they should be withdrawn.

A. The High Prevalence of Expression of CD20 Antigen in CLL Patients Is Not Equivalent to High Levels of Expression of the CD20 Antigen on CLL Cells in a Patient

At page 5 of the Final Action, the Examiner states that Kaminski discloses "high expression of CD20 on CLL (more than 95% expression on patients with CLL)." The Examiner cites this observation in Kaminski to support her conclusion that the prior art would have led a person of ordinary skill in the art to conclude that effective treatment of NHL using anti-CD20 antibodies would have established a reasonable expectation that effective treatment of CLL would result from administrating anti-CD20 antibodies to CLL

patients. See Final Action at page 5. Dr. Schenkein explains in his second declaration why this is not correct.

Dr. Schenkein explains that, while most CLL cells (i.e., >95%) express some CD20 antigen, the density of expression of these antigens on CLL cells is low, especially compared to NHL cells. In other words, while the CD20 antigen can be detected on many CLL cells, the level or density of expression of this antigen on any individual CLL cell is low, particularly as compared to the level or density of expression of the CD20 antigen on individual NHL cells. Moreover, as Dr. Schenkein has explained, this low density or "dim" CD20 antigen expression was known to be a distinguishing feature of CLL cells at the time of the invention. Schenkein 2nd at ¶¶ 7-8 and Almasri (1992) cited therein.

B. The Low Density of Expression of CD20 on CLL Cells Would Have Led the Skilled Person to Doubt that One Could Effectively Treat CLL With Anti-CD20 Antibodies

As noted above, the Examiner has made a factual error in concluding that individual CLL cells express "high levels" of CD20 antigen. In reality, the literature shows that CLL cells have a low density or "dim" expression of CD20 antigens on individual CLL cells. This attribute of CLL cells would have led a person of ordinary skill in the art, armed with knowledge about how anti-CD20 antibodies provide effective treatment of NHL, to doubt that CLL could be effectively treated with anti-CD20 antibodies.

Dr. Schenkein explains why this is the case. As he explains, the high density of expression of CD20 on NHL cells was believed to be an important reason why anti-CD20 antibodies are able to effectively kill NHL cells. He points out that the high CD20 antigen density on NHL cells enables the anti-CD20 antibodies to mediate effective cell killing via antibody-dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) mechanisms in the patient treated with the antibody. See Schenkein 2nd ¶ 9.

Dr. Schenkein then explains that the low level of CD20 antigen expression on individual CLL cells would have been seen as preventing effective ADCC and CDC-mediated cell killing by anti-CD20 antibodies. Schenkein 2nd, ¶10. Dr. Schenkein cites two scientific publications (Farag and Golay), each of which confirms that the low density of expression of CD20 on CLL cells significantly reduces the capacity of anti-CD20 antibodies to mediate both ADCC and CDC of such cells. See Schenkein 2nd at ¶¶ 11-12. As Dr. Schenkein concludes:

> Therefore, even though greater than 95% of CLL patients express *some* CD20 antigen on their neoplastic cells, this would not have provided an oncologist in 1998 with a legitimate scientific basis for believing that an anti-CD20 antibody could be used to effectively treat patients with CLL. Instead, in 1998, an oncologist would have believed that the low density of expression of CD20 would have been the relevant factor, because it would render these neoplastic cells in the CLL patient not susceptible to ADCC and CDC – two mechanisms of action believed to be important to the way that anti-CD20 antibodies provided therapeutic effectiveness against neoplastic cells in NHL patients.

See Schenkein 2nd at ¶13.

C. The High Tumor Cell Burden in CLL Patients Would Have Led The Skilled Person to Further Doubt that CLL Patients Could be Effectively Treated Using Anti-CD20 Antibodies

Dr. Schenkein has explained that the high number of circulating tumor cells in CLL patients create a "sink" of CD20-binding sites in CLL patients, and that a person of ordinary skill in the art would have assumed this phenomenon would have prevented anti-CD20 antibodies from providing effective treatment of CLL patients . See Schenkein 2nd at ¶ 15; Schenkein 1st at ¶ 22. Despite recognizing that this evidence was provided in the last response (see Final Action at page 3), the Examiner fails to respond to or otherwise address it in the Final Action.

Dr. Schenkein explains in greater detail in his second Declaration the basis of his conclusion that the high tumor cell burden in CLL patients would have led a person to believe that administration of anti-CD20 antibodies to a CLL patient would not provide effective treatment of the patient. See Schenkein 2nd at ¶¶ 14-16. As he explains, at the time of the invention, ADCC and CDC were believed to be important mechanisms in

the way that anti-CD20 antibodies kill cells in NHL therapy. See Schenkein 2nd at ¶ 9. He then explains that a person of ordinary skill would have doubted that a CLL patient's immune system could support the ADCC and CDC necessary to provide therapeutic effects seen in treatment of NHL using anti-CD20 antibodies. See Schenkein 2nd at ¶ 15. Dr. Schenkein also cites Kennedy, which identifies concerns over the capacity of the immune systems of CLL patients to support effective clinical responses mediated by anti-CD20 antibodies, noting in particular: "(i) the treatment would consume so much complement that the ability of the antibody to promote CDC could be compromised, (ii) the capacity of the mononuclear phagocytic system (MPS) to remove IgG-opsonized cells might be exceeded at high cell counts, and (iii) Fcγ receptor mediated rearrangement and capping of antibody-antigen complexes on the surface of B-cells might lead to removal of the complexes, thus allowing cells to escape.") See Schenkein 2nd at ¶ 16. Compare to Schenkein 1st at ¶ 30, discussing high levels of malignant CD20+ cells in CLL patients and effect in creating "huge sink" of CD20 binding sites in the blood of CLL patients.

Thus, Applicant has provided substantial scientific evidence that identifies two distinct reasons why a person of ordinary skill in the art prior to the present invention would have doubted that anti-CD20 antibodies would be effective in treating CLL patients. Indeed, the knowledge in 1998 about how rituximab provided therapeutic benefits in treatment of NHL patients, coupled with knowledge of the differences between these diseases, is the basis for why a person of ordinary skill in the art would not have expected benefits to result from administration of an anti-CD20 antibody like rituximab to CLL patients.

Applicant respectfully submits that the essential reasoning of the Examiner in support of the rejections conflicts with these well-supported scientific explanations. In particular, the Examiner has reached incorrect conclusions about the meaning and significance of certain evidence (e.g., the density of expression of CD20 on CLL vs. NHL cells, and the significance of that fact) or has simply failed to address the evidence that was earlier provided (e.g., the significance of the high tumor burden in CLL patients). Accordingly, Applicant submits that the rejections of the record under § 103

do not have a legitimate scientific or factual foundation, and should be reconsidered and withdrawn.

V. Different Antitumor Mechanisms and Significant Differences in the Impact of Therapy Do Exist Between NHL and CLL

In maintaining the rejections, the Examiner has cited the absence of evidence establishing that the "immunotherapeutic mechanisms, host effector functions and receptor binding affinity of the CD20 antibody would differ between the two diseases [NHL and CLL] resulting in different antitumor mechanisms and significant differences in the impact of therapy." See Final Action at page 6. Applicant submits that this evidence has been provided in Dr. Schenkein's first and second declarations under 37 C.F.R. § 1.132 and in the various scientific publications cited in these declarations.

As Dr. Schenkein explains in his second declaration, the way in which anti-CD20 antibodies provide therapeutic benefits in CLL patients differs substantially from the way anti-CD20 antibodies provide therapeutic benefits in NHL patients. In particular, Dr. Schenkein explains that:

- Anti-CD20 antibodies such as rituximab were thought to kill B-cells via CDC and ADCC (Schenkein 2nd ¶ 9);
- High-density expression of CD20 on NHL cells was needed for such CDC and ADCC (Schenkein 2nd ¶ 9);
- CLL cells were known to dimly express CD20 antigen, particularly as compared to NHL cells (Schenkein 2nd ¶ 8);
- Such low CD20 expression would significantly reduce the susceptibility of CLL cells to ADCC (Schenkein 2nd ¶ 11);
- Such low CD20 would further significantly reduce the susceptibility of CLL cells to CDC (Schenkein 2nd ¶¶ 11-12);
- CLL cells also overexpress complement inhibitors, CD55 and CD59, and those complement inhibitors further reduce CDC. (Schenkein 2nd ¶ 12);
- CLL patients have significantly higher tumor burdens than NHL patients (Schenkein 2nd ¶ 15); and

- CDC would be seriously compromised because of such high tumor burdens (Schenkein 2nd ¶ 16).

This scientific evidence clearly shows that the immunotherapeutic mechanisms, host effector functions and receptor binding affinity of anti-CD20 antibodies, in fact, do differ substantially between NHL and CLL treatment methods using anti-CD20 antibodies.

Dr. Schenkein also explains why Kaminski, alone or in conjunction with any of the other references, provides no basis for concluding that the immunotherapeutic mechanisms of action and relevance of CD20 antigen binding by anti-CD20 antibodies in treatment of NHL would be the same as those in anti-CD20 antibody treatment of CLL. See Schenkein 2nd at ¶19-24. In particular, he points out that an oncologist would have recognized that the guidance provided in Kaminski concerned radioimmunotherapeutic methods for treating lymphomas, and that these methods employ a fundamentally different mechanism of action to provide therapeutic results relative to how unlabeled anti-CD20 antibodies provide therapeutic benefits (i.e., the radioisotope kills cells via exposure to radiation, whereas an immune response is directed against cells via the unlabeled anti-CD20 antibody). See Schenkein 2nd at ¶ 19. Indeed, because of the "bystander effect," the particular tumor cell antigen, its level of expression and the nature of antibody binding to it become relatively unimportant factors in radioimmunotherapy methods, in contrast to the claimed therapeutic methods in which those factors are very important. Id.

Thus, as was the case with the primary references, the immunotherapeutic mechanisms of action, role of host effector functions, and significance of CD20 antigen binding in the treatment methods described in Kaminski differ substantially from those of the methods of treating CLL claimed in this application. As such, Kaminski would not have provided any basis for a person of ordinary skill to conclude that treatment of CLL using unlabeled anti-CD20 antibodies would have been expected to be successful at the time of the invention. See Schenkein 2nd ¶¶ 23-24.

VI. Factual Evidence of Failure in Attempts to Treat CLL Using Anti-CD20 Antibodies

At page 5 of the Final Action, the Examiner states "that there seems to be no factual evidence presented suggestive of failure of treatment of CLL in a patient." See Final Action at page 5. Applicant submits that substantial amounts of evidence have been provided that do, in fact, suggest that treatment of CLL by administration of anti-CD20 antibodies would not have been expected to be effective at the time of the invention. In addition, with this response, Applicant provides additional evidence of failed attempts to treat CLL using anti-CD20 antibodies.

Initially, the Examiner has improperly reversed the burden of proof on this issue. Well-established law requires the Examiner to demonstrate that the prior art would not only have suggested the claimed invention, but would establish in the mind of the person of ordinary skill in the art a reasonable expectation that the invention would work as claimed. It does not require an Applicant to prove that, before the invention was made, efforts to actually practice the invention were undertaken and failed.

Applicant nevertheless has established that, prior to the date of this invention, a person of ordinary skill in the art (i.e., an oncologist with experience in treating CLL patients) would have had several substantial reasons to doubt that CLL patients could be effectively treated using anti-CD20 antibodies. Dr. Schenkein's first and second declarations identify and explain with corresponding support in the literature why this is the case.

Dr. Schenkein's personal experiences are also relevant in this regard. As he points out, he was actually treating CLL patients in 1998 when rituximab was approved for treatment of NHL patients. He explains that despite the availability of rituximab at that time, he did not give it to his CLL patients. He cites the significant differences between the diseases, the unique characteristics of neoplastic CLL cells, and concerns about serious adverse side effects, as the basis for his belief then that rituximab would not provide therapeutic benefits for his CLL patients. See Schenkein 2nd ¶ 26. This personal experience of Dr. Schenkein is highly pertinent to, and contradicts, the

Examiner's assertions regarding the beliefs of a person of ordinary skill in the art at the time of the invention. Given that Dr. Schenkein is qualified to describe the views of a skilled artisan from his personal experience, this evidence should be given substantial weight by the Examiner.

Dr. Schenkein also provides in his second declaration further evidence supporting his conclusions. In particular, he discusses the clinical report found in Jensen *et al.*, *Ann. Hematol.* 77: 89-91 (1998), previously cited and considered by the Examiner. See PTO Form 1449 initialed 11 April 2008 and entered in the file on 29 May 2008; Interview Summary dated 5 October 2006.. In Jensen, the authors administered rituximab to a CLL patient at the dose used for NHL patients. The authors report that this patient not only exhibited a severe adverse reaction – rapid tumor lysis syndrome – but also report that the treatment was "*ineffective*." See Schenkein 2nd ¶ 29. In particular, Jensen reports that the patient failed to exhibit a positive clinical response to the treatment (i.e., the patient exhibited signs of progression of the disease after treatment requiring salvage chemotherapy). See Jensen at page 90, column 2 and Schenkein 2nd ¶ 29. The Jensen authors also refer to minor "clinical side effects" in six additional CLL patients, and do not report that the antibody achieved a positive clinical benefit in those patients either. Schenkein 2nd ¶ 32.

Thus, Applicant not only has provided substantial scientific evidence showing why a person of ordinary skill in the art would not have had reasonable expectation that administration of anti-CD20 antibodies to CLL patients would provide effective treatment of those patients, but has also provided evidence of failed attempts to treat CLL with anti-CD20 antibodies.

VII. The Claims Require Positive Clinical Effects from Treatment

At page 6 of the Final Action, the Examiner asserts that the term "treatment reads broadly on a process of implementing therapy to modify, alter or remedy a health problem." The Examiner makes this observation after stating that "while declarant suggests that there would be decreased therapeutic efficacy that suggestion is not equivalent to there would be *no* therapeutic effectiveness." Final Action at page 5.

Applicant submits that the Examiner has not correctly construed the requirements of the present claims, nor has she properly understood the testimony provided in Dr. Schenkein's first declaration.

The present claims all specify treatment of a CLL patient by administering an anti-CD20 antibody "*in an amount effective to treat the chronic lymphocytic leukemia*" The claims as drafted, thus, require *effective* treatment of CLL.

As Dr. Schenkein points out, the specification explains that effective treatment of CLL "must result in a positive clinical benefit to the CLL patient." See Schenkein 2nd at ¶ 33. Dr. Schenkein then points to specific portions of the patent specification which support his opinion. As he explains:

> My opinion of what this expression in the claims would convey to an oncologist is consistent with the specification of the '347 application, which refers to treatment methods that result in, for example, demonstrated efficacy with minimal infusion-related toxicity (page 8, paragraph 0320), overall response rate (ORR), complete responses (CR), partial responses (PR), improved median time to progression or improved duration of response (page 9, paragraph 0340 as well as page 14, paragraph 0440), or remission upon treatment (page 11, paragraph 0370).

See Schenkein 2nd at ¶ 34. Thus, contrary to the Examiner's conclusions, the claims do require a specific, positive therapeutic outcome, and not simply induction of any type of response in the patient. Certainly, the requirements of the claims are not met by Jensen, as by no measure can an undesirable and life-threatening condition in the CLL patient, coupled with a "continued progression of the CLL disease" be considered an effective treatment of CLL. See, Schenkein 2nd, ¶ 33.

The Examiner has also misinterpreted Dr. Schenkein's earlier testimony in reaching her conclusion about "decreased therapeutic effectiveness." Dr. Schenkein in his first declaration did not state that administration of an anti-CD20 antibody to a CLL patient would provide a lower degree of therapeutic effectiveness relative to the degree of success in treatment of NHL patients. Instead, he explained the factors that would have led a person of ordinary skill in the art to expect that administration of an anti-CD20 antibody to a CLL patient would not have been effective to treat a CLL patient.

See, e.g., Schenkein 1st at ¶¶ 16, 31. Dr. Schenkein's opinions were based on his analysis of the significant differences between NHL and CLL, and the implications of those differences for the potential ability of an anti-CD20 antibody to provide a clinical benefit in a CLL patient. Dr. Schenkein in his second declaration provides more specific explanations why, in 1998, a person of ordinary skill in the art would not have believed administration of an anti-CD20 antibody would have provided positive clinical benefits to a CLL patient.

Accordingly, Applicant submits that the Examiner's conclusions that the prior art would have rendered the claimed methods of treating CLL, especially when properly construed, obvious to a person of ordinary skill in the art are contradicted by the evidence provided by Applicant.

VIII. The Claimed Invention is Therapeutically Effective and Satisfies a Long Felt Need

The claimed treatment regimes described in the present application are effective in treating CLL. For example, in his second declaration, Dr. Schenkein presents phase III clinical trial results showing the effectiveness of the claimed methods for treating CLL. Dr. Schenkein also explains that the treatment methods "address a long felt need for a safe and effective way to treat CLL patients" (Schenkein 2nd ¶ 36), including a way to effectively treat fludarabine-refractory patients who "had no viable alternative treatment options in 1998" (Schenkein 2nd ¶ 37). Finally, Dr. Schenkein explains that CLL treatment with an anti-CD20 antibody is a "significant medical breakthrough" that will be practice-changing, providing the standard of care for CLL patients in the future. Schenkein 2nd ¶ 38. Aside from further demonstrating the effectiveness of the claimed methods, the evidence provided by Dr. Schenkein in his second declaration constitute secondary evidence of non-obviousness, including the claimed invention's ability to address "long felt but unsolved needs" in the treatment of CLL.

IX. Conclusion

For the reasons set forth above, applicant requests that the examiner reconsider and withdraw all of the outstanding rejections under § 103.

Applicant believes that the application is in condition for allowance. Should the examiner have any remaining questions or concerns, she is invited to contact the undersigned at the telephone number below.

Respectfully submitted,

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